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In re Application of:

Applicant: **Canadian Blood Services et al.**

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Serial No.: **PCT/CA2005/000472**

Title: **METHOD FOR TREATING AUTOIMMUNE DISEASES WITH ANTIBODIES**

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AMENDMENT/RESPONSE UNDER ARTICLE 34 PCT

Sir:

In response to the Written Opinion mailed July 27, 2005, please amend the application as follows:

In the Specification

Please replace pages 2, 27, 28 and 29 originally filed in this application with amended pages 2, 27, 28 and 29 attached hereto.

In the Claims

Please replace claim pages 32 to 38 originally filed in this application with amended claim pages 32 to 38 attached hereto.

REMARKS

Independent method claims 1 and 17 have been amended to further define the soluble antigen, and thus, Applicant believes these and subsequently dependent claims patentably distinguish over the teachings of D1, D2 or D3. Support for a soluble antigen of the present claims that is immunologically inert can be found on page 3, line 7.

In addition, claims 30 and 44 are amended to specify preferred embodiments wherein of the present invention for treating immune thrombocytopenia or arthritis is provided.

Clerical errors noted on pages 2, 27, 28 and 29 are also herein amended. On page 2, a typographical error resulted in the inadvertent omission of the word "can" at line 17. This is herein amended. In respect of pages 27, 28 and 29, Applicant respectfully submits that Figure 14 was mentioned therein in error, and in fact 13 Figures in total appear on 14 sheets in connection with the present invention. As a result, these pages have been amended to provide correct references to the figures, as originally filed.

In view of the preceding comments and amendments, Applicant believes the present application is in favour of a positive International Preliminary Report on Patentability.

Respectfully submitted,

Canadian Blood Services et al.

By _____
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The present study was undertaken to investigate if antibodies to soluble antigens could inhibit autoimmune diseases.

SUMMARY OF THE INVENTION

According to the present invention, a novel method for treating an autoimmune disease is provided. Furthermore, a novel mechanism of action has been established in accordance with the present invention for antibody-based treatment regimes for autoimmune disease, including, but not limited to anti-CD44 and soluble antigen specific antibody treatment regimes.

In one embodiment of the invention there is provided a method for treating autoimmune diseases in a mammal which method comprises administering to the mammal an effective amount of at least one antibody specific for a soluble antigen.

Different types of autoimmune diseases can be treated by the method of the present invention. According to the present invention, an autoimmune disease includes, but is not limited to Immune thrombocytopenia, Immune cytopenia, Idiopathic thrombocytopenic purpura (ITP), Neuropathy, Chronic inflammatory demyelinating polyneuropathy (CIDP), Guillain-Barre syndrome (GBS), Kawasaki's disease, Dermatomyositis, SLE, Myasthenia gravis, Post-transfusion purpura, Rheumatoid arthritis, Inflammatory arthritis, Eaton-Lambert syndrome,toxic epidermal necrolysis, and polymyositis.

In one embodiment, the treatment can be effected for a time and under conditions sufficient to inhibit platelet clearance, thereby treating or ameliorating an autoimmune disease such as immune thrombocytopenic purpura (ITP), for example. In a further embodiment, inflammatory arthritis can

experimental evidence that the antibody-based treatment regimes of the present invention, induce a priming event in innate leukocytes which endows leukocytes with the ability to ameliorate or inhibit autoimmune disease, specifically in ITP, thrombocytopenia, or in inflammatory arthritis, joint inflammation. We call this effect "IVIg-mediated cellular programming" (IMCP). This term is intended to more broadly refer to an antibody-mediated cellular programming effect, however for simplicity reference is made to the IVIg example, and hence IMCP is used throughout without prejudice. It is not intended to restrict the effect to only IVIg treatment regimes.

A monoclonal antibody (anti-CD44) is also demonstrated to inhibit immune thrombocytopenia by the same mechanism (ie. an IMCP-like effect in Figure 11. Here, anti-CD44 + leukocytes were incubated for 30 min, unbound anti-CD44 was washed off, leukocytes were then injected into ITP mice, and an amelioration of thrombocytopenia resulted. Mice in the first column (Nil) were uninjected. Mice in the second column (ITP) were treated with anti-platelet antibody (αCD41) only. On Day 1, mice in the third and fourth column (IMCP) were injected intravenously with splenic leukocytes (106/mouse) that went through the IMCP process with IVIg or anti-CD44 for 30 min. On Day 2 mice in columns (second to fourth) were injected with 2 µg anti-platelet antibody. On Day 3, all mice were bled for platelet enumeration as described (Blood 105:1546-1548, 2005).

Figure 12 illustrates an antibody-mediated cellular programming effect, herein referred to as IMCP, as mentioned above, at work in splenic leukocytes incubated with monoclonal anit-OVA, thus establishing a basis for the mode of action of the treatment regimes of the present invention. As illustrated, anti-ovalbumin + ovalbumin + leukocytes are

incubated for 30 min, unbound anti-ovalbumin and ovalbumin are washed off, and leukocytes are injected into ITP mice to provide ameliorating effect against thrombocytopenia in vivo. According to Figure 12, mice in the first column (Nil) were uninjected. Mice in the second column (ITP) were treated with anti-platelet antibody (αCD41) only. On Day 1, mice in the third column (IVIg) were injected with 50 mg/ml of dialyzed IVIg. Mice in the fourth column were injected (i.v.) with 1 mg OVA that had been pre-incubated with 50 µg of monoclonal anti-OVA (IgG1, clone OVA-14 Sigma). Mice in the fifth column were treated as in fourth column except with control mouse IgG (mouse IgG, Cat# 10400, Caltag) in place of monoclonal anti-OVA. Mice in the sixth column (IMCP) were injected intravenously with splenic leukocytes (106/mouse) that went through the IMCP process with dialyzed IVIg for 30 min. Mice in the seventh column were treated with splenic leukocytes (106/mouse) that went through IMCP process with 1 mg OVA that had been pre-incubated with 50 µg of monoclonal anti-OVA for 30 min. Mice in the eigth column were treated as in seventh column except with control mouse IgG in place of monoclonal-anti-OVA. On Day 2, mice in columns (second to eigth) were injected with 2 µg anti-platelet antibody. On Day 3, all mice were bled for platelet enumeration as described (Blood 102:558-560, 2003).

IVIg, anti-CD44 (KM-114), and antibody to soluble antigens (in the presence of the soluble antigen) cannot ameliorate thrombocytopenia in mice which are genetically deficient in the inhibitory Fcγ receptor (FcγRIIB) Interestingly, however, we show here that these same antibodies can, all ameliorate thrombocytopenia when they are pre-incubated with leukocytes isolated from mice that are genetically deficient in FcγRIIB (FcγRIIB$^{-/-}$) and the FcγRIIB$^{-/-}$

leukocytes are injected into wild type mice. Thus, the IMCP effect as herein reported can work where leukocytes do not express an FcgammaRIIB receptor. Although, FcgammaRIIB receptor expression was required in the recipient in order to achieve IMCP. In the reverse of this experiment (where the leukocytes are from FcγRIIB$^{+/+}$ mice and the recipient mice are FcγRIIB$^{-/-}$), again, IVIg, anti-CD44, and anti-soluble antigen (+ the antigen) all cannot ameliorate the thrombocytopenia (Figure 13). As shown in Figure 13, mice in the 1st column (Nil-BL/6) are uninjected C57BL/6 mice. Mice in the 2nd column (CD41-BL/6) were C57BL/6 mice treated with anti-platelet antibody (αCD41) only. Mice in the 8th column (Nil-RIIB) were uninjected FcγRIIB$^{-/-}$ mice. Mice in the 9th column (CD41-RIIB) were FcγRIIB$^{-/-}$ mice treated with anti-platelet antibody (αCD41) only. On Day 1, mice in the 3rd column (IVIG-BL/6) were injected with 50 mg/ml IVIg. Mice in the fourth column (IVIG-BL/6) were C57BL/6 mice injected intravenously with splenic leukocytes (10^6/mouse) from C57BL/6 mice that went through the IMCP process with IVIg for 30 min. Mice in the 5th column (IVIG-RIIB) were FcγRIIB$^{-/-}$ mice injected intravenously with splenic leukocytes (10^6/mouse) from C57BL/6 mice that went through the IMCP process with IVIg for 30 min. Mice in the 6th column (BSA-RIIB) were FcγRIIB$^{-/-}$ mice injected intravenously with splenic leukocytes (10^6/mouse) from C57BL/6 mice that went through the IMCP process with BSA for 30 min. Mice in the 7th column (BSA-BL/6) were C57BL/6 mice injected intravenously with splenic leukocytes (10^6/mouse) from C57BL/6 mice that went through the IMCP process with BSA for 30 min. Mice in the 10th column (IVIG-RIIB) were injected with 50 mg/ml IVIg. Mice in the 11th column (IVIG-BL/6) were C57BL/6 mice injected intravenously with splenic leukocytes (10^6/mouse) from FcγRIIB$^{-/-}$ mice that went through the IMCP process with IVIg for 30 min. Mice in the 12th column (IVIG-RIIB) were FcγRIIB$^{-/-}$ mice